PROCESS FOR PRODUCING INDENOL ESTERS OR ETHERS

Technical Field

The present invention relates to the field of organic synthesis. More particularly it provides a process for making an indenol ester or ether from an α-substituted cinnamic aldehyde derivative such as an acetal or an acylal. This reaction is promoted by the use of strong mineral acids, sulphonic acids, acidic zeolites or Lewis acids.

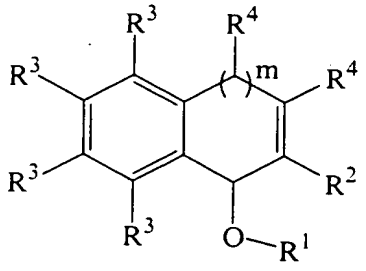
Background

The organic compounds of formula (I), as defined below, can be useful as perfuming ingredients or as starting material for the synthesis of compounds having a more complex skeleton. The methods of preparation of such compounds as reported in the prior art are in general quite long and/or expensive. Thus, there is a need for improved processes for preparing such compounds.

It would be highly desirable to access such compounds by means of a simple and efficient isomerization process wherein the starting material is an easily accessible material. To the best of our knowledge, there is no report in the prior art of an isomerization process giving a direct access to compounds of formula (I) from the compound of formula (II).

Summary of the Invention

In order to solve the problems aforementioned, a first embodiment of the present invention provides a process for making a compound of formula



(I)

wherein m is 0, 1 or 2;

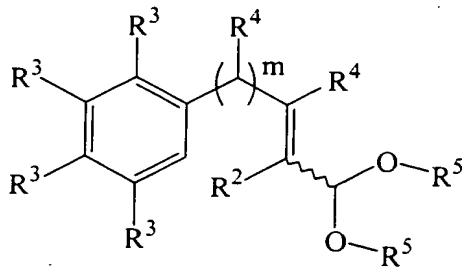
R^1 represents a formyl group, a -COCOOH group or a group of formula $-(CO)_n$-R-T, in which n is 0 or 1, R is a C_6H_4 group, C_{1-5} alkanediyl or alkenediyl group and T is OH, COOH or a hydrogen atom;

R^2 represents a C_{1-6} alkyl or alkenyl group;

at least one R^3 represents a hydrogen atom and the other R^3 represent each a hydrogen atom or a C_{1-5} alkyl, alkenyl or alkoxy group; and

R^4 represents a hydrogen atom, a phenyl group or a R^2 group;

comprising the cyclization, at a temperature above 10° C, of the corresponding compound of formula



(II)

wherein each R^5, taken separately, represents a formyl group or a $-(CO)_n$-R-H group, or the R^5, taken together, represent a $-(CO)_n$-R-$(CO)_n$- group or a -COCO- group;

the wavy line indicates that the configuration of the carbon-carbon double bond is E or Z or a mixture thereof; and

m, n, R, R^2, R^3 and R^4 have the meaning as indicated above;

in the presence of a catalyst selected from the group consisting of strong mineral protic acids, sulphonic acids, acidic zeolites and Lewis acids.

For the invention purpose, it is important that R^2 is not a hydrogen atom, indeed if R^2 is H then the reaction does not take place.

According to an embodiment of the present invention, m is preferably 0 or 1, or even more preferably 0.

Furthermore, according to one of the above-described embodiments, R^1 may also represent a group of formula $-(CO)_n$-R-T, in which n is 0 or 1, R is a C_6H_4 group or a C_1-$C_{(5-n)}$ alkanediyl or alkenediyl group and T is OH, COOH or a hydrogen atom. Alternatively R^1 may also represent a group of formula $-(CO)_n$-R-T, in which n is 0 or 1, R is a C_1-$C_{(3-n)}$ alkanediyl group and T is OH, COOH or a hydrogen atom.

According to these embodiments R^2 may represent a C_{1-6} alkyl group.

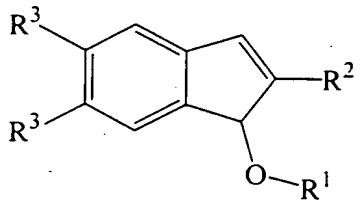
Moreover, in such embodiments, at least two R^3 may represent a hydrogen atom and the other R^3 may represent each a hydrogen atom or a C_{1-5} alkyl or alkoxy group.

Furthermore, R^4 may represent a hydrogen atom or a C_{1-6} alkyl group, and preferably is a hydrogen atom.

The invention also relates to certain compounds that are made by these processes.

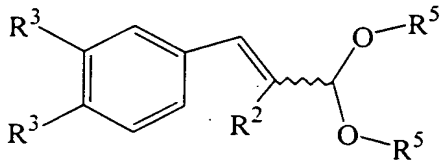
Detailed Description of the Preferred Embodiments

According to a particular embodiment of the invention the compounds of formula (I) are of formula



(I')

and are obtained by cyclization of the corresponding compounds of formula



(II)

wherein R^1, R^2, R^3 and R^5 have the same meaning as indicated above.

The compounds of formula (I') wherein one R^3 is a hydrogen atom and the other R^3 is a C_{1-5} alkyl group are new compounds and can be used as starting compounds for the synthesis of indenols. Amongst these compounds can be cited the 2-methyl, the 2,5-dimethyl or the 2,6-dimethyl derivatives of formula (I').

The catalyst, which can be used in the invention's process, is a strong mineral protic acid, a suphonic acid, an acidic zeolite or a Lewis acid. By "mineral" we mean here an acid having an anion which does not contain a carbon atom. By "strong" we mean here a protic acid having a $pK_{AB} < 3$, preferably below 2.

The catalyst can be in the anhydrous form or also in the hydrate form, except for those acids which are unstable in the presence of water.

According to another particular embodiment of the invention, the catalyst is selected from the group consisting of H_2SO_4, p-toluenesulphonic acid, $NaHSO_4$, $KHSO_4$, H_3PO_4, HCl, HNO_3, BF_3 and its adducts with C_{2-6} ethers or with C_{2-6} carboxylic acids, poly(styrene sulphonic acid) based resins, K-10 Clay, SnX_4, FeX_3 and ZnX_2, X representing a halogen atom, such as Cl or Br, or a C_{1-6} carboxylate, such as acetate or trifluoroacetate, or a C_{1-7} sulphonate, such as a triflate or tosylate.

Preferably, the catalyst is H_3PO_4, FeX_3 or ZnX_2.

The catalyst can be added to the reaction medium in a large range of concentrations. As non-limiting examples, one can cite catalyst concentrations ranging from 0.001 to 0.30 molar equivalents, relative to the molar amount of the starting compound (II). Preferably, the catalyst concentrations will be comprised between 0.005 and 0.15 molar equivalents. It goes without saying that the optimum concentration of catalyst will depend on the nature of the catalyst and on the desired reaction time.

Another parameter of the invention's process is the temperature. In order to allow the cyclization to occur, it is useful to carry out the invention's process at a temperature of at least 10°C. Below this temperature the speed of the reaction decreases quite rapidly. The upper limit of temperature range is fixed by the reflux temperature of the reaction mixture that, as skilled persons know, depends on the exact nature of the starting and final product and optionally, as explained below, of the solvent. However, as non-limiting example, one can cite a preferred temperature ranging between 60°C and 180°C. Of course, a person skilled in the art is also able to select the preferred temperature as a function of the melting and boiling point of the starting and final products as well as of the solvent.

The process of the invention can be carried out in the presence or in the absence of solvent. As a person skilled in the art can anticipate, the presence of a solvent is mandatory only in the case in which the starting compound is a solid compound under the reaction conditions.

According to a preferred embodiment of the invention, and independently of the physical state of the starting compound, the process is advantageously carried out in the presence of a solvent. Preferably, the solvent is anhydrous or does not contain more than 5% w/w water.

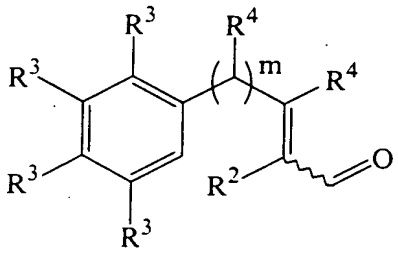
Non-limiting examples of such a solvent are C_4-C_8 ethers, C_3-C_6 esters, C_3-C_6 amides, C_6-C_9 aromatic solvents, C_5-C_7 linear or branched or cyclic hydrocarbons, C_1-C_2 chlorinated solvents and mixtures thereof.

Furthermore, the reaction can also be carried out in the presence of a solvent belonging to the family of carboxylic anhydride of formula $R^2C(O)O(O)CR^2$, R^2 being defined as above, optionally containing the corresponding carboxylic acid R^2COOH.

The compound of formula (II) can be made and isolated according to any prior art method. Alternatively, compound (II) can be also generated *in situ*, i.e. in the reaction medium just before its use, according to any know prior art method.

In particular, preferably the compound of formula (II) is made or generated by a method using the corresponding enal as starting material. Indeed, the enal can be easily obtained by an aldolic condensation, as a person skilled in the art knows well.

Therefore, another object of the present invention is an invention's process, as defined above, further comprising the step of generating *in situ* the compound of formula (II) starting from the corresponding enal of formula



(III)

wherein R^2, R^3, R^4 and R^5 have the same meaning indicated above.

A process comprising the *in situ* generation of the compound of formula (II) is particularly useful when the compound (II) is an acetal or an acylal, the latter being a geminal dicarboxylate.

Now, when the compound of formula (II) is an acylal, we have also noticed that the catalysts that are able to promote the cyclization of the acylal are also useful to promote the conversion of the enal into the corresponding acylal.

Therefore, another object of the present invention, and in fact a particular embodiment of the above-mentioned process, is a process for making an ester of formula (I), as defined above, comprising the step of reacting, in the presence of a catalyst

as defined for the cyclization step, an enal of formula (III), as defined above, with a carboxylic anhydride of formula $R^7C(O)O(O)CR^7$, wherein R^7, taken separately, represents a R^2 group as defined above or the R^7, taken together, represent a R group as defined above.

Examples

The invention will now be described in further detail by way of the following examples, wherein the abbreviations have the usual meaning in the art, the temperatures are indicated in degrees centigrade (°C). The NMR spectral data were recorded in $CDCl_3$ at 400MHz or 100MHz for ^1H or ^{13}C, respectively, the chemical displacements δ are indicated in ppm with respect to TMS as standard, and the coupling constants J are expressed in Hz. All the abbreviations have the usual meaning in the art.

Example 1

Cyclization of 2-alkylcinnamic aldehyde via the acylal derivative

a) *Preparation of 2-pentyl-1H-inden-1-yl acetate*

4.13 ml of a 0.25 M solution of $FeCl_3 6H_2O$ in Ac_2O (1.03 mmol) where diluted into Ac_2O (30.2 g) and the resulting solution was added dropwise during 1 hour to a stirred solution of 2-pentylcinnamaldehyde (20 g, 99 mmol) in AcOH (18.5 g) at reflux.

After a further 2 hours at reflux the cooled mixture was poured into a mixture of H_2O and Et_2O. Then, solid Na_2CO_3 (44.7 g) was added portionwise to the stirred mixture. After one hour stirring the aqueous phase was saturated with NaCl and extracted with Et_2O. The organic layers were dried over anhydrous Na_2SO_4, and the solvent evaporated to afford a crude product, which was further purified by distillation in vacuum to give the desired compound (yield = 87%).

B.p. 86-93°/0.05 mbar

^1H-NMR: 0.90(br.t,J=7,3H) ; 1.35(4H) ; 1.58(m,2H) ; 2.17(s,3H) ; 2.29(m,2H) ; 6.21(s,1H) ; 6.43(s,1H) ; 7.09(dd,J=7, J=7, 1H) ; 7.13(d,J=7,1H) ; 7.23(m,1H) ; 7.37(d,J=7,1H)

^{13}C-NMR: 171.4(s) ; 149.2(s) ; 143.7(s) ; 142.0(s) ; 128.9(d) ; 128.2(d) ; 125.1(d) ; 124.2(d) ; 120.4(d) ; 77.5(d) ; 31.6(t) ; 28.2(t) ; 27.7(t) ; 22.5(t) ; 21.1(q) ; 14.0(q)

b) *Preparation of 2-hexyl-1H-inden-1-yl acetate*

Using the same experimental procedure as under a), 2-hexylcinnamaldehyde (20 g, 92.6 mmol), $FeCl_3 6H_2O$ (3.85 ml of a 0.25 M solution in Ac_2O, 0.96 mmol), Ac_2O (28.3 g, 0.28 mol) in AcOH (17.4 g) were reacted together. After a further 3 hours at reflux the cooled mixture was treated to the same workup as before to provide the title compound (yield = 83%)

B.p. 89-101° / 0.035 mbar

^{1}H-NMR: 0.89(t,J=7,3H) ; 1.25-1.40(6H) ; 1.58(m,2H) ; 2.17(s,3H) ; 2.29(m,2H) ; 6.21(s,1H) ; 6.43(s,1H) ; 7.09(dd,J=7,J=7, 1H) ; 7.13(d,J=7,1H) ; 7,22(m,1H) ; 7.36(d,J=7,1H)

^{13}C-NMR: 171.4(s) ; 149.3(s) ; 143.7(s) ; 142.0(s) ; 128.9(d) ; 128.2(d) ; 125.1(d) ; 124.2(d) ; 120.4(d) ; 77.5(d) ; 31.7(t) ; 29.1(t) ; 28.3(t) ; 28.0(t) ; 22.6(t) ; 21.1(q) ; 14.1(q)

c) *Preparation of 2-methyl-1H-inden-1-yl acetate*

Using the same experimental procedure as under a), 2-methylcinnamaldehyde (21 g, 0.14 mol) in AcOH (27 g), $FeCl_3 6H_2O$ (6 ml of a 0.25 M solution in Ac_2O, 1.5 mmol) in Ac_2O (53 g) were reacted together. After a further 2 hours at reflux the cooled mixture was treated to the same workup and purification as before to provide the title compound (yield = 70%)

B.p. 70-95°/0.04 mbar.

^{1}H-NMR: 1.98(s,3H) ; 2.18(s,3H) ; 6.15(s,1H) ; 6.41(s,1H) ; 7.09(dd,J=7, 7, 1H) ; 7.12(d,J=7,1H) ; 7.23(m,1H) ; 7.37(d,J=7,1H)

^{13}C-NMR: 171.5(s) ; 144.4(s) ; 143.7(s) ; 142.1(s) ; 129.3(d) ; 128.9(d) ; 125.1(d) ; 124.2(d) ; 120.3(d) ; 78.4(d) ; 21.1(q) ; 14.0(q)

Example 2

a) *Preparation of 1-methoxy-2-methyl-1H-indene via cyclization of the acetal*

A solution of $FeCl_3$ anhydrous (42 mg, 0.25 mmol) in BuOAc (4 ml) was added dropwise during 10 minutes to a stirred solution of the 3,3-dimethoxy-2-methyl-1-phenyl-1-propene (5 g, 24.7 mmol) in BuOAc (13 ml) at 123° C. After 3 hours the cooled mixture was diluted with Et_2O (50 ml) and washed with saturated aqueous

$NaHCO_3$ and brine. Extraction, drying over anhydrous Na_2SO_4, concentration and fractional distillation in vacuum gave a crude product that was further purified by chromatography (SiO_2, cyclohexane/AcOEt 95:5 then AcOEt/Et_2O 1:1). There was thus obtained the title compound with a yield of 33%.

B.p. 32-43°/0.07 mbar

^{1}H-NMR: 2.03(s,3H) ; 3.03(s,2H) ; 4.85(s,1H) ; 6.44(s,1H) ; 7.09(dd,J=7,J=7, 1H) ; 7.11(d,J=7,1H) ; 7,22(m,1H) ; 7.41(d,J=7,1H)

^{13}C-NMR: 145.9(s) ; 143.9(s) ; 141.8(s) ; 128.7(d) ; 128.4(d) ; 124.6(d) ; 123.7(d) ; 120.1(d) ; 84.9(d) ; 51.8(q) ; 14.1(q)

b) *Preparation of 2-methyl-1H-inden-1-yl acetate via cyclization of the acylal*

A solution of $FeCl_3$ anhydrous (21 mg, 0.125 mmol) in BuOAc (2 ml) was added dropwise during 5 minutes to a stirred solution of the 2-methyl-3-phenyl-2-propenylidene diacetate (3.1 g, 12.5 mmol) in BuOAc (8 ml) at 123°. After 2 h at 123° the reaction was stopped and worked-up as above. Chromatography (SiO_2, cyclohex/AcOEt 9:1) of the crude product allowed the isolation of the title acetate (62% yield). Identical spectra as previously described.

Example 3

Synthesis of 2,6-dimethyl-1H-inden-1-yl acetate from the corresponding aldehyde

A solution of (2*E*)-2-methyl-3-(4-methylphenyl)-2-propenal (100.0 g, 0.62 mol) in cyclohexane (300.0 g) was added dropwise in 2 hours to a stirred solution of zinc chloride (3.1 g, 22 mmol) in acetic anhydride (188.4 g, 1.85 mol) at 80°C. The reaction mixture was stirred further at 80°C for 18 hours and then cooled to 25°C. The mixture was washed twice with water (100.0 g) and a 5% aqueous solution of sodium carbonate (100.0 g) and concentrated under reduced pressure. The crude product was flash-distilled (B.p.: 75-90°C / 0.1 mbar) affording 88.5 g of the desired acetate (69%) as a yellow liquid (purity: 97.1% GC).

^{1}H-NMR: 7.19 (s, H); 7.03 (d, J = 7.9, H); 6.99 (d, J = 7.9, H); 6.37 (s, H); 6.11 (s, H); 2.31 (s, 3 H); 2.17 (s, 3 H); 1.95 (s, 3 H).

^{13}C-NMR: 171.5 (*s*); 143.3 (*s*); 142.3 (*s*); 141.0 (*s*); 134.8 (*s*); 143.3 (*s*); 129.2 (*d*); 125.2 (*d*); 120.0 (*d*); 78.4 (*d*); 21.3 (*q*); 21.1 (*q*); 14.0 (*q*).

Example 4

Synthesis of 2,6-dimethyl-1H-inden-1-yl acetate from the corresponding aldehyde

General procedure

A solution of (2*E*)-2-methyl-3-(4-methylphenyl)-2-propenal (100.0 g, 0.62 mol) in acetic anhydride (100.0 g) was added dropwise in 2 hours to a stirred solution of the catalyst in acetic anhydride (88.4 g, 1.85 mol in total) at 80°C. The reaction mixture was stirred further at 80°C until the complete conversion of the starting material and then cooled to 25°C. The mixture was diluted with methyl *tert*-butyl ether (300.0 g), washed successively with water (twice 100.0 g) and a 5% aqueous solution of sodium carbonate (100.0 g) and concentrated under reduced pressure. The crude product was flash-distilled (B.p.: 75-90°C / 0.1 mbar) affording the desired acetate as a yellow liquid.

The results obtained are listed in the following table:

Catalyst	Reaction time	Isolated yield
H_3PO_4 (0.072 eq.)	22 h.	51%
$BF_3.OEt_2$ (0.036 eq.)	19 h.	37%
$ZnBr_2$ (0.036 eq.)	5 h.	55%

eq. = molar equivalents in respect to the starting material h = hours

Example 5

Synthesis of 1-ethoxy-2-butyl-1H-indene from the corresponding aldehyde

A mixture of 2-butylcinnamic aldehyde (5 g, 26.7 mmol.), triethyl orthoformate (5.9 g, 40 mmol.), absolute ethanol (10 g, 217 mmol.) and Amberlyst® 15 (0.52 g) was heated at reflux (85°C oil bath). After three days, the mixture was filtered and concentrated under vacuum. The residue was subjected to silica gel flash chromatography (hexane/ethyl acetate 98:2), yielding 3.8 g (17.6 mmol., 66% yield) of the indenyl ethyl ether.

^{1}H-NMR: 0.95 (t, J=7.4, 3H), 1.15 (t, J=6.9, 3H), 1.46-1.36 (m, 2H), 1.70-1.50 (m, 2H), 2.45-2.30 (m, 2H), 3.27-3.15 (m, 2H), 4.95 (s, 1H), 6.41 (s, 1H), 7.1 (t, J=7.2, 1H), 7.13 (d, J=7.2, 1H), 7.21 (t, J=7.2, 1H), 7.42 (d, J=7.2, 1 H).

^{13}C-NMR: 14.0 (q), 15.7 (q), 22.7 (t), 28.1 (t), 30.5 (t), 60.0 (t), 83.4 (d), 120.2 (d), 123.7 (d), 124.6 (d), 126.9 (d), 128.3 (d), 142.5 (s), 143.6 (s), 151.3 (s).